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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,476	DUBRIDGE, ROBERT B.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006 and 31 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/2006 has been entered.

Receipt is acknowledged of an amendment, filed 8/31/2006, in which claims 1-65 were canceled, and claims 66-83 were newly added. Currently, claims 66-83 are pending.

Any rejection of record in the previous office actions not addressed herein is withdrawn.

Election/Restrictions

Applicant elected Group I without traverse in the reply filed 3/18/2005. Applicant confirmed the provisional election of Flp recombinase as the species of recombinase in the reply filed 11/29/2005. All pending claims are readable upon the elected invention.

Currently, claims 66-83 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 5 is vague and indefinite in that the metes and bounds of the phrase "selected from the group consisting of mammalian cells, yeast cells, and/or bacterial cells" are unclear. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). In the instant case, the scope of the host cell is unclear. It is unclear if the cell types are being claimed in the alternative form, or if the claim encompasses mammalian and bacterial host cells together, for example. It would be remedial to amend the claim language to clearly indicate that the host cell is selected from the group consisting of mammalian cells, yeast cells, and bacterial cells."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 66 and 70-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051, cited in a prior action; see the entire reference) in view of Seibler et al (Biochemistry, Vol. 36, pages 1740-1747, 1997, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 6/1/2005 and has been altered to clarify the rejection and address the amendments to the claims in the reply filed 8/31/2006.

Regarding claim 66, Cheo et al teach an integration cassette (e.g. starting molecule or Destination vector) comprising two recombination sites flanking promoters, selectable markers, and tags such histidine tags or green fluorescent protein (e.g. paragraphs [0045], [0050], [0147], [0148], [208] and [0488]; Figure 6). Cheo et al define the term "selectable marker" to mean a nucleic acid segment that allows one to select for or against a molecule or cell that contains it, often under particular conditions, including nucleic acid segments that encode products which can be readily identified (e.g., phenotypic markers such as P-galactosidase, green fluorescent protein (GFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), cyan fluorescent protein (CFP), and cell surface proteins (paragraph [0258]). Further, Cheo et al teach the addition of regions that allow integration into eukaryotic chromosomes (e.g. transposable elements) (e.g. paragraph [0327]). As a general rule, the insertion of transposons into target DNA is a random event (e.g. paragraph [0010]). Cheo et al teach a first target cassette comprising a polynucleotide to be substituted into the integration cassette flanked by two recombination sites (e.g. paragraphs [0045] and [0075]). Regarding the recombination sites and additional vectors, Cheo et al teach the following:

> In another specific aspect, the invention provides a method of cloning comprising providing at least a first nucleic acid molecule comprising at least a

> first and a second recombination site and at least a second nucleic acid molecule comprising at least a third and a fourth recombination site, wherein none of the first, second, third or fourth recombination sites is capable of recombining with any of the other sites, providing one or more vectors (e.g., two, three, four, five, seven, ten, twelve, etc.), comprising at least a fifth, sixth, seventh and eighth recombination site, wherein each of the fifth, sixth, seventh and eighth recombination sites are capable of recombining with one of the first, second, third or fourth recombination site, and conducting a recombination reaction such that at least said first and second molecules are recombined into said vectors. See paragraph [0154].

See also Figures 6 and 7 and paragraph [0075], for example. Further, Cheo et al teach a recombinase activity capable of recognizing the recombinase recognition sites of the second integration cassette and second target cassette (e.g. paragraphs [0055], [0196], [0253] and [0295]). Cheo et al teach the use of the Flp recombinase protein to catalyze recombination between Frt sites (e.g. paragraphs [0047], [0048], [0055] and [0253]).

Regarding claim 70, Cheo et al teach the use of mammalian cells, yeast cells and bacterial cells (e.g. paragraph [0436]). Thus, the integration cassette would be capable of integrating in mammalian, yeast or bacterial cells.

Regarding claim 71, Cheo et al teach the use of a first integration cassette comprising two, three, four etc. open reading frames that further comprise sequences that function as internal ribosome entry sites (IRES) (e.g. paragraph [0147]). The IRES allows the expression of two structural genes from a single transcript (i.e. bi-cistronic element) (e.g. paragraph [0544]).

Regarding claim 72, Cheo et al teach the use of a first integration cassette comprising a gene encoding a fusion protein comprising an N- or C-terminal tag such as an epitope tag or a six histidine tag (e.g. paragraph [0062]).

Regarding claim 73, Cheo et al teach a first target cassette comprising a first target gene and a first selectable marker gene that may be the same or different marker as compared to a selectable marker in the first integration cassette (e.g. paragraphs [0046] and [0148]).

Regarding claim 74, Cheo et al teach a first target cassette further comprising a plolycistronic element by including an IRES sequence to permit the bi-cistronic expression of two gene products from a single promoter (e.g. paragraphs [0143] and [0544]).

Regarding claim 75, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0034]).

Regarding claim 76, Cheo et al teach a second integration cassette comprising a gene encoding a fusion protein comprising an N- or C-terminal tag such as an epitope tag or a six histidine tag (e.g. paragraph [0062]).

Regarding claim 77, Cheo et al teach a second integration cassette comprising two, three, four etc. open reading frames that further comprise sequences that function as internal ribosome entry sites (IRES) (e.g. paragraph [0147]). The IRES allows the expression of two structural genes from a single transcript (i.e. bi-cistronic element) (e.g. paragraph [0544]).

Regarding claim 78, Cheo et al teach a second target cassette comprising a first target gene and a first selectable marker gene that may be the same or different marker as compared to a selectable marker in the second integration cassette (e.g. paragraphs [0046] and [0148]).

Regarding claim 79, Cheo et al teach a second target cassette further comprising a plolycistronic element by including an IRES sequence to permit the bi-cistronic

expression of two gene products from a single promoter (e.g. paragraphs [0143] and [0544]).

Regarding claim 80, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0034]).

Regarding claim 81, Cheo et al teach the use of the system of claim 66 (described above) with nucleic acid molecules encoding more than one subunit of a multi-subunit complex such as an enzyme (e.g. paragraphs [0168] and [0354]).

Regarding claim 82, Cheo et al teach the use of the system of claim 66 (described above) with nucleic acid molecules encoding a multi-subunit complex that comprises an antibody molecule (e.g. paragraph [0168]).

Regarding claim 83, the recombination sites of the vectors function as "cloning sites" to clone recombinant molecules. Further, Cheo et al teach the inclusion of one or more restriction sites (e.g. multiple cloning sites) in the nucleic acid cassettes of the invention (e.g. paragraph [0140]).

Cheo et al do not teach a rec element encoding at least one flp recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette.

Seibler et al teach a rec element, plasmid pOG44, encoding flp recombinase activity (e.g. page 1741, *(d) Recombination Prior to Integration*). Seibler et al teach a first integration cassette, a first target cassette and a rec element. Seibler et al teach a first integration cassette (P construct) comprising an FTR site interposed between an SV40 promoter and a bicistronic expression unit consisting of the SEAP and HygTk genes followed by a second FRT site

different from the first FRT site (e.g. Figure 2; paragraph bridging pages 1742-1743). The first integration cassette is capable of random integration into the genome of a cell (e.g. page 1741, *Transfection (Stable Expression)*). Seibler et al teach a first target cassette (promoter-free exchange plasmid) comprising a bicistronic expression unit, consisting of the luciferase and puromycin resistance genes, flanked by FRT sites capable of recombining with the first and second FRT sites of the first integration vector (e.g. Figure 2; paragraph bridging pages 1742-1743). Seibler et al tech the use of a Flp recombinase activity in mammalian cells (e.g. Table 1; Figure 1; page 1741, *(d) Recombination Prior to Integration*; Figure 3). Seibler et al teach that mammalian cells are capable of supporting recombinase mediated cassette exchange (RMCE), which will provide advantages including the ability to create reference integration sites characterized by their expression potential and long-term stability (e.g. page 1747, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to the cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Seibler et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in mammalian cells and Seibler et al teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in mammalian cells.

One would have been motivated to make such a modification in order to receive the expected benefit of identifying reference integration sites in the mammalian genome for reproducible levels of expression as taught by Seibler et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the

contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 66 and 70-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051, cited in a prior action; see the entire reference) in view of Cox et al (US Patent No. 6,140,129, cited in a prior action; see the entire reference). This rejection has been included to address embodiments not covered by the combination of references set forth above. This rejection was made in the Office action mailed 6/1/2006 and has been altered to address Applicant's amendment to the claims in the reply filed 1/29/2005.

The teachings of Cheo et al are described in the above rejection and are applied as before.

Cheo et al do not teach a rec element encoding flp recombinase activity.

Cox et al teach a rec element encoding flp recombinase activity for expression in bacteria (e.g. column 6, lines 38-43). Further, the FLP system of Cox et al provides a method that can regulate recombination events and introduce FRT targets virtually anywhere in the chromosome (e.g. column 2, lines 6-14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Cox et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in bacterial cells and Cox et al

teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in bacterial cells.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to regulate flp-mediated recombination events virtually anywhere in the bacterial chromosome as taught by Cox et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 66-68 and 70-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051, cited in a prior action; see the entire reference) in view of Seibler et al (Biochemistry, Vol. 36, pages 1740-1747, 1997, cited in a prior action; see the entire reference) and Ow (US Patent Application Publication No. 2002/0123145, cited in a prior action; see the entire reference). This is a new rejection.

The teachings of Cheo et al are described in the above rejection and are applied as before.

Cheo et al do not teach a rec element encoding at least one flp recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette. Cheo et al do not teach the inclusion of the rec element in the first integration cassette or the first target cassette.

Seibler et al teach a rec element, plasmid pOG44, encoding flp recombinase activity (e.g. page 1741, *(d) Recombination Prior to Integration*). Seibler et al teach a first integration cassette, a first target cassette and a rec element. Seibler et al teach a first integration cassette (P

construct) comprising an FTR site interposed between an SV40 promoter and a bicistronic expression unit consisting of the SEAP and HygTk genes followed by a second FRT site different from the first FRT site (e.g. Figure 2; paragraph bridging pages 1742-1743). The first integration cassette is capable of random integration into the genome of a cell (e.g. page 1741, *Transfection (Stable Expression)*). Seibler et al teach a first target cassette (promoter-free exchange plasmid) comprising a bicistronic expression unit, consisting of the luciferase and puromycin resistance genes, flanked by FRT sites capable of recombining with the first and second FRT sites of the first integration vector (e.g. Figure 2; paragraph bridging pages 1742-1743). Seibler et al tech the use of a Flp recombinase activity in mammalian cells (e.g. Table 1; Figure 1; page 1741, *(d) Recombination Prior to Integration*; Figure 3). Seibler et al teach that mammalian cells are capable of supporting recombinase mediated cassette exchange (RMCE), which will provide advantages including the ability to create reference integration sites characterized by their expression potential and long-term stability (e.g. page 1747, left column).

Ow teaches a first integration cassette, first target cassette and rec element. Ow teaches a first integration cassette (receptor construct) comprising a promoter operably linked to a first exchangeable reporter segment comprising a thymidine kinase (tk) coding region and a zeocin resistance coding region, wherein the tk coding sequence is linked to a first recombinase recognition site (PP') at its 5' end and to a second recombinase recognition site at its 3' end (PP') (e.g. Figure 4). More generally, Ow teaches integration cassettes comprising a polynucleotide flanked by two irreversible recombination sites (IRSs), which are stably integrated into the genome of a host organism (e.g. paragraphs [0014] and [0042]). Because the cassettes do not comprise sequence homologous to a chromosome of the target organism, integration will be

random. Ow teaches a first target cassette (donor construct) comprising a third recombinase recognition site (BB'), capable of recognizing the first recognition site in the first integration cassette; a first target element (cDNA); and a fourth recombinase recognition site (BB'), capable of recognizing the second recombinase recognition site in the first integration cassette (e.g. Figure 4). More generally, Ow teaches target cassettes comprising a polynucleotide flanked by two irreversible complementary recombination sites (CIRSs) (e.g. paragraphs [0014] and [0042]). Ow teaches a rec element encoding a recombinase polypeptide capable of catalyzing a recombination reaction between IRS and CIRS, wherein introduction of the rec element and the first target cassette to the recombinant cell population comprising the first integration cassette results in site-specific substitution of the first exchangeable reporter segment with the first exchangeable target segment (e.g. Figure 4, paragraphs [0014], [0037] and [0054]). Ow teaches that the rec element (polynucleotide encoding the recombinase) can be included in the first integration cassette (receptor construct) containing the IRSs (e.g. paragraphs [0045] and [0054]). Ow teaches that the rec element can be included in the first target cassette (donor construct) containing the CIRSs (e.g. paragraph [0054]). Ow teaches the use of the abovementioned system in host cells such as mammalian cells, fungi and bacteria. Ow teaches a first target element further comprising a first target gene and a first selectable marker gene (e.g. paragraphs [0060] and [0180]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to the cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Seibler et al because Cheo et al teach it is within the

ordinary skill in the art to perform recombination reactions *in vivo* in mammalian cells and Seibler et al teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in mammalian cells. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the rec element in the first integration cassette or first target cassette, because Cheo et al and Ow et al teach is it within the skill of the art to use recombinase activity to perform site specific recombination and exchange of nucleic acid segments.

One would have been motivated to make such a modification in order to receive the expected benefit of identifying reference integration sites in the mammalian genome for reproducible levels of expression as taught by Seibler et al. Further, one would have been motivated to include the rec element in either the first integration cassette or first target cassette in order to receive the expected benefit of having a system where fewer nucleic acid molecules need to be introduced into the cell in order to support the desired recombination method. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 66 and 69-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051, cited in a prior action; see the entire reference) in view of Seibler et al (Biochemistry, Vol. 36, pages 1740-1747, 1997, cited in a prior action; see the entire reference) and Ogilvy et al (Blood, Vol. 94, No. 6, pages 1855-1863, 1999; see the entire reference). This is a new rejection.

The teachings of Cheo et al are described in the above rejection and are applied as before.

Seibler et al teach a rec element, plasmid pOG44, encoding flp recombinase activity (e.g. page 1741, *(d) Recombination Prior to Integration*). Seibler et al teach a first integration cassette, a first target cassette and a rec element. Seibler et al teach a first integration cassette (P construct) comprising an FTR site interposed between an SV40 promoter and a bicistronic expression unit consisting of the SEAP and HygTk genes followed by a second FRT site different from the first FRT site (e.g. Figure 2; paragraph bridging pages 1742-1743). The first integration cassette is capable of random integration into the genome of a cell (e.g. page 1741, *Transfection (Stable Expression)*). Seibler et al teach a first target cassette (promoter-free exchange plasmid) comprising a bicistronic expression unit, consisting of the luciferase and puromycin resistance genes, flanked by FRT sites capable of recombining with the first and second FRT sites of the first integration vector (e.g. Figure 2; paragraph bridging pages 1742-1743). Seibler et al tech the use of a Flp recombinase activity in mammalian cells (e.g. Table 1; Figure 1; page 1741, *(d) Recombination Prior to Integration*; Figure 3). Seibler et al teach that mammalian cells are capable of supporting recombinase mediated cassette exchange (RMCE), which will provide advantages including the ability to create reference integration sites characterized by their expression potential and long-term stability (e.g. page 1747, left column).

Ogilvy et al teach an hCD4 reporter to facilitate mammalian cell-by-cell analysis (e.g., by flow cytometry) (e.g. page 1855, Materials and Methods; page 1857, left column, 1st full paragraph; Fig 1D and E). Ogilvy et al teach that the CD4 reporter was chosen because its molecular interactions have been well characterized and monoclonal antibodies are available that recognize it specifically (e.g. page 1857, left column 1st full paragraph). Ogilvy et al teach the

reporter cassette bound by FRT sites to provide the option of Flp-mediated recombination to aid in replacing the hCD4 reporter by another gene.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to the cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Seibler et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in mammalian cells and Seibler et al teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in mammalian cells. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the hCD4 reporter taught by Ogilvy et al in the integration cassette of Cheo et al, because Cheo et al teach the inclusion of phenotypic markers such as cell surface proteins, and Ogilvy et al teach the use of hCD4 as a cell surface reporter in a cassette flanked by FRT recombination sites.

One would have been motivated to make such a modification in order to receive the expected benefit of identifying reference integration sites in the mammalian genome for reproducible levels of expression as taught by Seibler et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. Further, one would have been motivated to use the hCD4 reporter of Ogilvy et al because it allows cell-by-cell analysis, its molecular interactions have been well characterized, and monoclonal antibodies are available that recognize it specifically.

Response to Arguments - 35 USC § 103

With regard to the rejection of claims 66 and 70-83 under 35 U.S.C. 103(a) as being unpatentable over Cheo et al in view of Seibler et al, Applicant's arguments filed 8/18/2006 have been fully considered but they are not persuasive.

The response asserts that the combined teachings of Cheo et al and Seibler et al fail to teach or suggest all of the limitations recited in new claims 66-83. The response asserts that the following elements are not taught by the references: (i) scorable homeostatic reporter element comprising at least one scorable reporter gene, and (ii) vectors that are capable of random insertion into a discrete genomic position in a host cell.

The instant specification defines the term "scorable homeostatic reporter element to mean both genetic traits and the genes that encode traits whose presence can be physically or chemically detected and quantified without adversely affecting the viability of the cell expressing the homeostatic reporter element (paragraph [56]). Cheo et al define the term "selectable marker" to mean a nucleic acid segment that allows one to select for or against a molecule or cell that contains it, often under particular conditions, including nucleic acid segments that encode products which can be readily identified (e.g., phenotypic markers such as P-galactosidase, green fluorescent protein (GFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), cyan fluorescent protein (CFP), and cell surface proteins (paragraph [0258]). Accordingly, the selectable markers taught by Cheo et al encompass phenotypic markers that meet the definition of scorable homeostatic reporter elements of the instant specification and claims. Therefore, Cheo et al teach vectors comprising scorable homeostatic reporter elements. Further, Seibler et al teach the use of a nucleic acid sequence encoding SEAP in the integration cassette. This is a

secreted alkaline phosphatase (e.g. page 1740, right column, footnote) that is capable of being assayed without lysing the cells. The response asserts that the luciferase reporter taught by Seibler et al is luciferase, which is detected by assaying extracts obtained from lysed cells. It is noted that the luciferase reporter of Seibler et al is used in the target cassette, which is not required to contain a homeostatic reporter element.

The assertion that the vectors taught by Cheo et al are not capable of random integration into a discrete genomic position is not found persuasive. The instant specification defines the term "random" to include "pseudo-random" insertion, where certain insertion sites are preferred over insertion generally into the endogenous DNA, provided the reference is not exclusive to a small subset of sites. Cheo et al teach the use of transposons, which are generally randomly inserted in the genome (e.g. paragraph [0010]). Furthermore, Cheo et al teach the vectors in linear form and circular form (e.g. paragraphs [0045] and [0052]). Seibler et al teach that the introduction of DNA into mammalian cells can result in random integration of the DNA (e.g. paragraph bridging pages 1742-1743). Moreover, Applicant has indicated in prior remarks that the vectors of Cheo et al will randomly integrate into the genome (page 23, paragraph 1 of the remarks filed 11/29/2005). Accordingly, the vectors taught by Cheo et al are capable of random integration at discrete positions of the genome.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With regard to the rejection of claims 66 and 70-83 under 35 U.S.C. 103(a) as being unpatentable over Cheo et al in view of Cox et al, Applicant's arguments filed 8/18/2006 have been fully considered but they are not persuasive.

The response asserts that the references do not teach integration vectors comprising at least one scorable homeostatic reporter element comprising at least one scorable reporter gene.

The instant specification defines the term "scorable homeostatic reporter element to mean both genetic traits and the genes that encode traits whose presence can be physically or chemically detected and quantified without adversely affecting the viability of the cell expressing the homeostatic reporter element (paragraph [56]). Cheo et al define the term "selectable marker" to mean a nucleic acid segment that allows one to select for or against a molecule or cell that contains it, often under particular conditions, including nucleic acid segments that encode products which can be readily identified (e.g., phenotypic markers such as P-galactosidase, green fluorescent protein (GFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), cyan fluorescent protein (CFP), and cell surface proteins (paragraph [0258]). Accordingly, the selectable markers taught by Cheo et al encompass phenotypic markers that meet the definition of scorable homeostatic reporter elements of the instant specification and claims. Therefore, Cheo et al teach vectors comprising scorable homeostatic reporter elements.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Applicant's arguments, see pages 10-11, filed 8/18/2006, with respect to the rejection of claims 2-5, 8, 11, 14 and 19 under 35 U.S.C. 103(a) as being unpatentable over Ow in view of

Schlake et al have been fully considered and are persuasive. The references do not teach integration vectors comprising at least one scorable homeostatic reporter element comprising at lest one scorable reporter gene. The previous rejection of claims 2-5, 8, 11, 14 and 19 has been withdrawn.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER